TESTIMONY OF JOSEPH A. DIMASI, PH.D.

DIRECTOR OF ECONOMIC ANALYSIS

TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT

TUFTS UNIVERSITY, BOSTON, MASSACHUSETTS

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IMPROVING THE NEW DRUG DEVELOPMENT PROCESS

SUMMARY OF STATEMENT

In this testimony, I will present data and analyses on the length of the clinical development and regulatory approval processes for new drugs. Specifically, I will show results from analyses of the time from synthesis, first testing in humans anywhere in the world, and filing of an investigational new drug application to approval of a new drug application for new chemical entities (NCEs). Data will also be presented on the length of the approval process for new drugs in the United States. The information relied upon in this testimony was obtained from Tufts Center for the Study of Drug Development databases that track new drug development and approval times for NCEs approved in the United States since 1963. While substantial progress has been made in reducing new drug approval times, the development period is so lengthy that legislative and administrative changes that may expedite the process should be examined.

Mr. Chairman and Members of the Subcommittee:

Thank you for the opportunity to speak to the Committee. My name is Joseph DiMasi. I am an economist and Director of Economic Analysis at the Tufts Center for the Study of Drug Development, a non-profit, policy research group affiliated with Tufts University.

Mr. Chairman, the new drug development process is lengthy, risky, and costly. It is imperative that the process be examined and optimized to the extent possible through legislative and other means so that patients may receive safe and effective therapies sooner than they have in the past. Discussions about policy reforms are best conducted when the facts about the process are known. For more than 20 years, the Tufts Center for the Study of Drug Development (CSDD) has provided data and analyses about new drug development and regulatory review with the hope that policy debates will be better informed.

In this testimony, I will present some of our latest results on the length of new drug development and regulatory approval for drugs approved in the United States. The data are obtained from a combination of public sources and surveys of the pharmaceutical industry conducted by the CSDD. The CSDD databases of approved drugs contains information on when certain development and regulatory milestones for new chemical entities (NCEs) are reached. Included in the database are NCEs approved since the 1962 Amendments to the *Federal Food Drug and Cosmetic Act*.

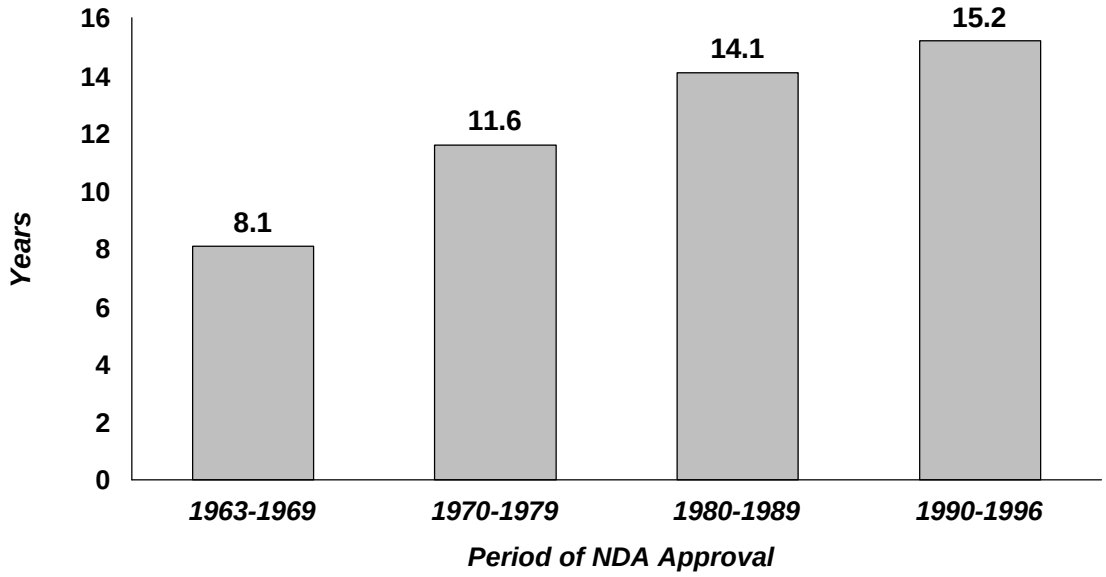
For purposes of this testimony, an NCE is defined as a new molecular compound not previously approved in the United States, excluding vaccines and diagnostic agents and new salts, esters, and dosage forms of previously approved compounds. Included are new therapeutic biologics that were reviewed by the Food and Drug Administration's (FDA's)

Center for Drug Evaluation and Research (CDER). This definition differs from the FDA definition of a new molecular entity (NME) primarily in that it excludes diagnostic drugs. The distinction may be justified, in part, in that the development and regulatory histories of diagnostics could differ somewhat from those of new therapeutic agents.

Discovery to Approval Time

The time from synthesis of a new drug to U.S. marketing approval is very lengthy and has increased over time. Our data indicate that this period has increased from approximately eight years for approvals in the 1960s to approximately 15 years for approvals in the 1990s (including preliminary data for the 1996 approvals). The lengthening of the period from discovery to approval has been associated, not surprisingly, with substantial increases in the cost of developing new drugs.[1] Lengthy development periods and high R&D costs provide disincentives for firms to innovate. Portions of this period and of the cost of R&D, however, have little or nothing to do with the behavior and policies of regulatory agencies. Generally, the strength of the relationship between regulation and these variables diminishes for earlier parts of the process. For example, regulatory practices and policies have much less impact on the preclinical portion of the discovery to approval period than on the clinical development portion. The regulatory authorithy's greatest degree of control is over the regulatory review phase.

Figure 1. Mean Time from Synthesis to NDA Approval, 1963 - 1996

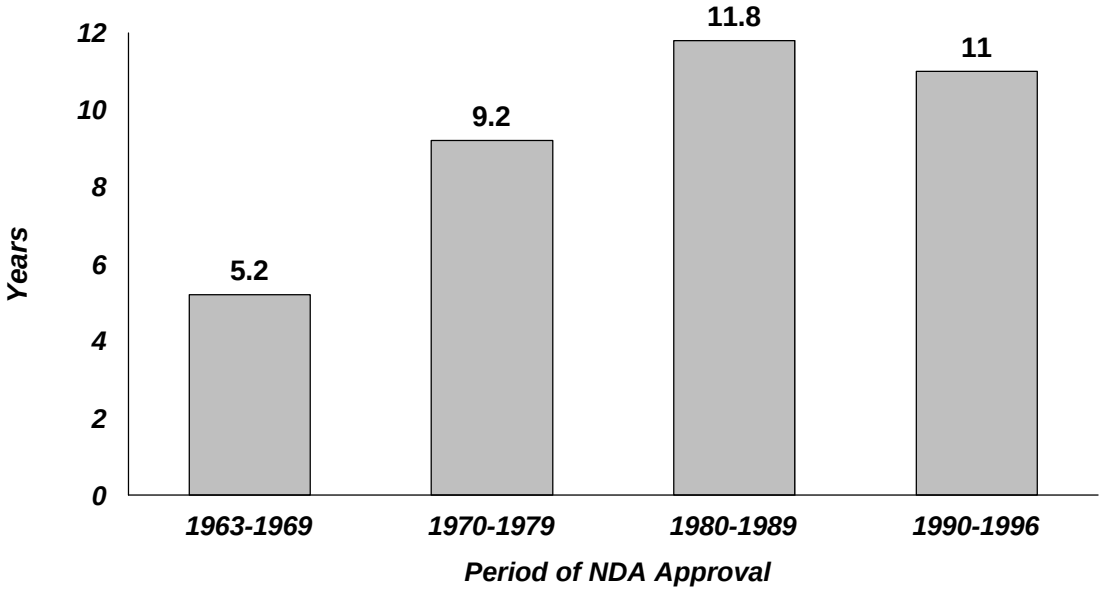


Source: Tufts CSDD Approved NCE Database, 1997

Clinical Development Time

CSDD survey data allow us to determine the length of the period from first testing in humans anywhere in the world to marketing approval for new drugs approved in the United States. Figure 2 shows that, on average, this phase has more than doubled since the 1960s. The mean time from first human testing to U.S. marketing approval increased from approximately five years for approvals in the 1960s to 11 or more years in the 1980s and 1990s. The reduction in mean time from first human testing to U.S. approval for the 1990s approvals relative to the 1980s approvals may reflect a trend toward increasing globalization in industry activities.

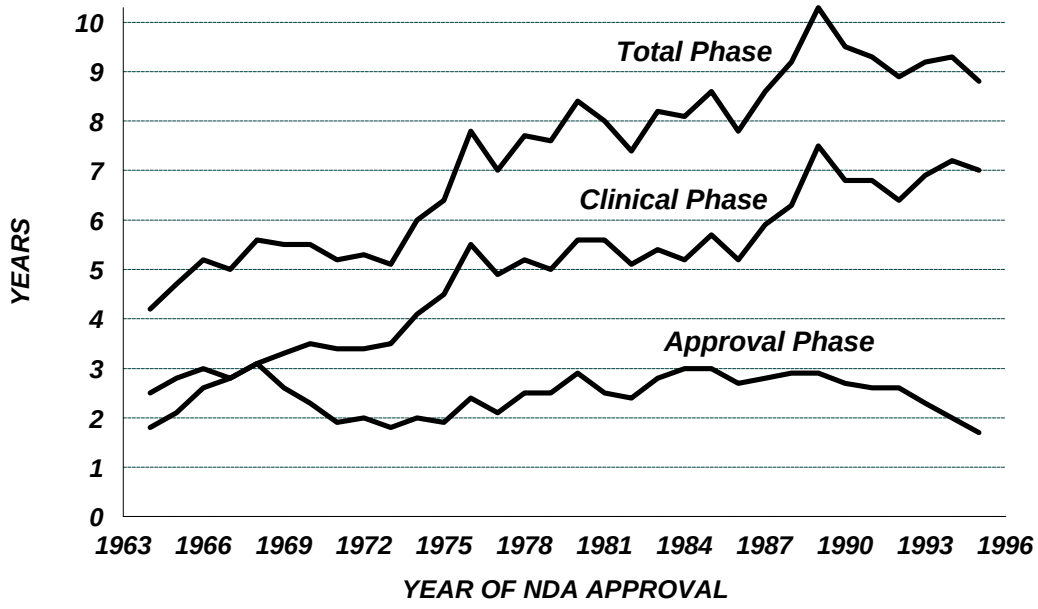
Figure 2. Mean Time from First Testing in Humans to NDA Approval, 1963 - 1996



Source: Tufts CSDD Approved NCE Database, 1997

The length of the U.S. portion of the clinical development process may be approximately measured by the time from the date that the first investigational new drug application (IND) was filed on an approved compound to the date on which the first new drug application (NDA) was submitted to the FDA. This period is depicted as the clinical phase in Figure 3. The total phase is the time from IND filing to NDA approval, while the approval phase is the time from NDA submission to NDA approval. The lines represent three-year moving averages. The average U.S. clinical phase has increased over time to approximately seven years for recent periods (the mean clinical phase for our preliminary data on the 1996 approvals is lower by about one year, but the average for the last three years is approximately seven years). The time that it takes to go from initial clinical testing in the United States to marketing approval has averaged about nine years for approvals in recent years.

Figure 3. Mean Approval, Clinical, and Total Phases for New Chemical Entity Approvals, 1963-1996



Source: Tufts Center for the Study of Drug Development, 1997

New Drug Approval Time and User Fees

The time from initial submission of an NDA to NDA approval generally had averaged approximately two and one-half years during the 1980s and early 1990s. Since 1994, average approval times have dropped substantially. The mean approval time for NCEs approved from 1994 to 1996 is 1.7 years. The *Prescription Drug User Fee Act of 1992*, or PDUFA has been credited with this recent dramatic reduction in new drug approval times. As you know, PDUFA authorizes the FDA to levy user fees on manufacturers who submit applications to the agency. Revenues are dedicated to the achievement of a set of specific performance goals, documented by then-FDA Commissioner Kessler and referenced in the Act. To provide an independent assessment of the impact of PDUFA on the new drug development process, the Tufts Center established an annual user fee survey of over 50 major pharmaceutical and

biotechnology firms with operations in the United States.

Our analyses focused on new chemical entities (NCEs) and a small number of biologics reviewed and approved by the FDA's Center for Drug Evaluation and Review. A cohort of user fee NCEs approved from 1993 through 1996 were compared with non-user fee NCEs approved from 1990 through 1992. Our soon-to-be-published results[2] show that the mean time from new drug application (NDA) submission to FDA approval was 53% shorter for user fee NCEs compared with non-user fee NCEs (14.5 months versus 31.0 months, respectively). This represents a considerable reduction in new drug approval times.

These findings support those in the FDA's Fourth Annual Performance Report to Congress[3] and demonstrate the impressive gains made by the FDA and the pharmaceutical industry in reducing NDA approval times. When the current results are viewed in the context of other FDA accomplishments -- such as accelerated review times for BLAs and efficacy supplements, a reduction in refusal-to-file notices, and the elimination of the formidable NDA backlog -- one can conclude that PDUFA has resulted in a notable improvement in FDA drug review activities. Moreover, approval times can be expected to decrease even further as the FDA strives to meet its PDUFA performance goals of 6-month review times of 90% of priority NDAs and 12-month review times for 90% of standard NDAs in fiscal year 1997.

Initiatives to Speed Development and Review

A number of initiatives and regulatory practices have been enacted in recent years that could conceivably have a positive impact on the length of the development and approval periods. The CSDD has analyzed a number of these policies in a series of studies.

FDA-Sponsor Meetings

Formal meetings between drug sponsors and the FDA during development and regulatory review can potentially reduce the time from initial clinical testing to marketing approval. The major objectives of these meetings are to optimize clinical trial design, to ensure that NDA submissions are adequately prepared, to familiarize reviewers with the nature of a forthcoming submission, and to resolve scientific and medical disputes efficiently. In a study to be published soon,[4] we have analyzed the impact of formal FDA-sponsor conferences on the length of the development and approval periods for NCEs approved from 1987 to 1995. Although some types of meetings have not been utilized often enough to allow us to find statistically significant associations, the associations between some meetings and development or approval times were strong. In particular, pre-IND meetings were associated with shorter clinical development times, and pre-NDA meetings were associated with shorter approval times.

Recent reports indicate that, as part of their PDUFA II discussions, the FDA and the pharmaceutical and biotechnology industries have tentatively agreed on policies for conducting formal meetings. Timelines for holding requested meetings have been promulgated. Pre-IND meetings and pre-NDA meetings have been singled out for faster than normal response times. In light of the results from our recent study, policies that encourage the timely use of FDA-sponsor meetings in general, and pre-IND and pre-NDA meetings in particular, will likely expedite development and approval.

Subpart E and Accelerated Approval

Over the past decade, the FDA has implemented two regulatory initiatives aimed at speeding the development and approval of drugs intended to treat life-threatening and seriously-debilitating conditions. The expedited development (Subpart E)[5] and the accelerated approval[6] regulations are intended to move drugs to market more quickly by compressing clinical development and FDA approval times. Both, to varying degrees, depart from traditional FDA standards for approval by invoking a less certain balancing of risks and benefits. The regulations are notable not only for their less onerous evidentiary standards; they also suggest a collaborative model of drug development that may serve the process well by increasing early communications between the sponsor and the FDA, raising the potential for greater efficiency by both parties.[7] A this point, it seems reasonable to inquire whether there are elements of these initiatives that could be applied more broadly to other categories of drugs and indications.

The Subpart E regulations call for broad flexibility in the application of established statutory standards, and for the adoption of a "medical risk-benefit" analysis that assumes a willingness on the part of desperately ill patients to accept more unknowns and thus a higher level of risk. Collaboration between the sponsor and the FDA, starting in the early preclinical phase, is the hallmark of the Subpart E model. For example, the regulations expressly call for pre-IND and end-of-phase I meetings between the sponsoring company and the agency. Other features of the Subpart E initiative include ongoing clinical trial monitoring and evaluation by the FDA, consideration of a treatment IND at the end of phase II, and the submission of the marketing application at the end of an expanded phase II clinical trial.

The more significant departure from traditional FDA evidentiary standards for drug approval is found in the accelerated approval regulations, the second of the two initiatives. The regulations permit marketing approval on the basis of changes in a surrogate endpoint. The link between those changes and actual clinical benefit need not be validated at the time of approval; instead, the anticipated benefits may be established in the post-approval period through phase IV confirmatory studies that are required as a condition of approval. The regulations provide for an expedited withdrawal procedure in six specific circumstances, including the failure of phase IV studies to generate evidence that the surrogate marker is a predictor of clinical benefit.

Most of the approvals under the accelerated approval initiative have involved AIDS therapies, but new drugs for cystic fibrosis, multiple sclerosis, and cancer have also been approved under the regulations. Although a recent statistical analysis of development and approval times did not show statistically significant effects for these two fast-track initiatives,[4] the number of approvals that have been granted under these regulations is relatively small and many of these compounds began development before the regulations were implemented. A more definitive empirical analysis of the impact of these regulations can be conducted after more compounds that have begun development subsequent to implementation of the regulations have proceeded to approval.

Computerization

In our recent study of factors that affect clinical development and approval times,[4] we found that computer-assisted new drug applications (CANDAs) were associated with shorter approval times. Although computerization of NDAs has increased notably over time, a

significant number of drugs approved in recent years have not had CANDA submissions. Our results, and continued advances in information technology, argue for increasing use of electronic submissions, as well as policies and funding that would allow the FDA to move to a paperless electronic information system for all submissions.

Conclusions

CSDD data show that the average time to get new drugs through development to approval has been lengthy. Noteworthy progress has been made in recent years in reducing approval times as the user fee program and management initiatives at the FDA have been successfully implemented. The clinical development period, however, is typically much longer than the regulatory approval period. Discussions of measures to bring new drugs to market sooner should consider policy changes that will speed clinical development, as well as maintain or improve upon the progress that has been achieved with respect to review times. The recent, and largely successful, efforts of the FDA and the pharmaceutical and biotechnology industries to reach agreement on reauthorization of the user fee program and on regulatory reforms designed to get safe and effective drugs to patients sooner indicate that substantial improvement can still be achieved.

References

1. DiMasi JA, Hansen RW, Grabowski HG, Lasagna L. Cost of innovation in the pharmaceutical industry. *Journal of Health Economics* 1991;10:107-142.
2. Kaitin KI. The Prescription Drug User Fee Act of 1992 and the new drug development process. *American Journal of Therapeutics* 1997; 4: in press.
3. Fourth Annual Performance Report: Prescription Drug User Fee Act of 1996: Fiscal Year 1996 Report to Congress. [Rockville MD]: Food and Drug Administration, Dec 1996.
4. DiMasi JA, Manocchia M. Initiatives to speed new drug development and regulatory review: the impact of FDA-sponsor conferences. *Drug Information Journal* 1997;31(3), in press.
5. 21 CFR 312.80 (Oct 1988).
6. 21 CFR 314:500 and 21 CFR 601.40 (Dec 1992).
7. Shulman SR, Brown JS. The Food and Drug Administration's early access and fast-track approval initiatives: how have they worked? *Food and Drug Law Journal* 1995;50:503-531.